UNITED STATES PATENT AND TRADEMARK OFFICE

C I C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,822	12/10/2001	Kevin P. Baker	GNE.2830P1C38	8184

30313 7590 10/06/2005

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,822	BAKER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

500

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Examination (RCE) filed on 21 July 2005 under 37 CFR 1.114 based on parent Application No. 10/015,822 is acceptable and an RCE has been established. An action on the RCE follows.

Status of Application, Amendments and/or Claims

The amendment of 21 July 2005 has been entered in full. Claims 28-32 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 28-35 and 38-40 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejections of claims 28-35 and 38-40 under 35 U.S.C. § 112, first paragraph (scope of enablement and written description) as set forth at pg 12-15 of the previous Office Action (25 April 2005) are *withdrawn in part* in view of cancelled claims 36-37 (02 February 2005) and the claim language of claims 33-34 and 38. Please see section on 35 U.S.C. § 112, first paragraph (scope of enablement and written description), below.

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

2. Claims 28-35 and 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth for claims 28-35 and 38-40 at pg 3-12 of

the previous Office Action (25 April 2005) and at pg 3-8 of the Office Action of 04 November 2004.

Specifically, claims 28-35 and 38-40 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown of SEQ ID NO: 374, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 374, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203465; wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. The claims also recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide.

Applicant's arguments (21 July 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

It is noted that at pages 6-8 and 15 of the Response, Applicant cites pertinent case law reviewing the legal standard of utility. The Examiner takes no issue with Applicant's general comments regarding the legal standard for utility.

(i) Applicant asserts that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1759 polypeptide. Applicant argues that it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is imperative to find evidence that protein levels can be accurately predicted. Applicant states that the question is not whether a necessary or even strong correlation between an increase

in copy number and protein expression levels exists, but whether it is more likely than not a person of ordinary skill in the art would recognize such as a positive correlation.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action of 25 April 2005, the instant specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon) (pg 517-519). However, there is no evidence regarding whether or not PRO1759 mRNA or polypeptide levels are also increased in these cancers. Furthermore, what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels (Pennica, et al, Proc. Natl. Acad. Sci., 95: 14717-14722, 1998).

As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (Journal of Proteome Research 2: 405-412, 2003) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (pg 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that twenty-eight of the 165 protein blots (17%) or 21 of 98

genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found (r= -0.025), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance.

As supported by the studies cited above, the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Madoz-Gurpide et al. (Adv Exp Med Biol 532: 51-58, 2003) even indicate that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels. A lack of correlation may imply that the predictive property of the gene(s) is independent of gene function" (pg 53, 1st full paragraph). Furthermore, Celis et al. (FEBS Lett 480 : 2-16, 2000) state that a complementary technology to DNA microarrays for monitoring gene expression is provided by proteomics (pg 6, last paragraph in col 1; see also Steiner et al. Electrophoresis 21: 2099-2104, 2000; pg 2100, col 1). However, the specification of the instant application has only disclosed that the PRO1759 polynucleotide is slightly overexpressed (about 2-fold) in 3 lung and colon tumor samples. The specification does not indicate that the PRO1759 polypeptide has been overexpressed in the lung and colon tumor samples tested. Celis et al. emphasize that proteins are frequently the functional molecules and, therefore, the most likely to reflect differences in gene expression (pg 6, bottom

of col 1). Celis et al. continue to explain that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2). Madoz-Gurpide et al. indicate that there is a need to utilize protein microarray strategies to address the many different features of proteins, including the determination of protein levels in biological samples (pg 53, 2nd full paragraph). There is also intense interest in the scientific field in applying proteomics to disease marker identification and such approaches include comparative analysis of protein expression in normal and cancer tissues to identify aberrantly expressed proteins that may represent novel markers (Madoz-Gurpide et al., pg 54, 2nd full paragraph).

Therefore, given the small increase in DNA copy number of PRO1759, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1759 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (*Brenner v. Manson* 1966, 383 U.S. 519, 148 USPQ 689).

(ii) Applicant contends that the Haynes data (cited by Examiner in previous Office Action) confirm that there is a general trend between protein expression and transcript levels, which

meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Applicant also points out that Haynes is not relevant to the current application because Haynes was studying yeast cells and not human cells. Applicant argues that Haynes did not compare mRNA expression levels and protein levels in the same yeast cells and thus the analysis by Haynes is not applicable to the present application.

Applicant's arguments have been fully considered but are not found to be persuasive. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Feroze-Merzoug et al. (Cancer and Metastasis Rev 20: 165-171, 2001) even disclose that "[t]he lack of correlation between mRNA and corresponding protein is evident even in low eukaryotic cells such as yeast. Therefore, it will be necessary to profile both mRNA and protein for a complete picture of how cells are altered during malignant transformation" (pg 168, col 1). Clearly, Haynes et al. and Feroze-Merzoug et al. indicate that mRNA levels do not predict protein levels.

(iii) At page 10 of the Response, Applicant further asserts that the analysis of Chen et al. is not applicable to the instant application. Applicant indicates that the proteins selected for study by Chen et al. were those detectable by staining on 2D gels. Applicant states that Chen et al. are likely to have excluded many of the proteins most likely to be significant as cancer markers. Applicant also argues that Chen et al. does not account for different expression in different

tissues or different stages of cancer. Applicant indicates that no attempt was made to compare expression levels in normal versus tumor samples and therefore, does not address the issue of whether increased mRNA levels in the tumor samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumorous versus normal tissue. Applicant concludes that in the Chen reference, even if the analysis presented is correct, a review of the correlation coefficient data presented in Chen et al. indicates that it is more likely than not that increased mRNA expression correlates with increased protein expression. At pages 11-12 of the response, Applicant discusses data from Tables I-II of Chen et al.

Applicant's arguments have been fully considered but are not found to be persuasive. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and polypeptide expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO1759 mRNA or polypeptide is overexpressed in lung or colon tumors, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

(iv) Applicant argues that the same authors as Chen et al. published a later paper (Beer et al., Nat Med 8(8): 816-824, 2002) which described gene expression of genes and adenocarcinomas and compared that to protein expression. Applicant concludes that the authors of the Chen et al. paper agree that microarrays provide a reliable measure of the expression levels of the gene and can be used to identify genes whose overexpression is associated with tumors.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Beer et al. generated gene-expression profiles for 86 primary lung adenocarcinomas, including 67 stage I and 19 stage III tumors, as well as 10 non-neoplastic lung samples (pg 816, col 1). Beer et al. determined transcript abundance using custom algorithms and the data set was trimmed of genes expressed at very low levels. Beer et al. used hierarchical clustering to examine similarities among lung adenocarcinomas in their patterns of gene expression and even identify "three clusters that showed significant differences with respect to tumor stage and tumor differentiation" (pg 822, 1st full paragraph). However, the specification of the instant application does not disclose any special feature, stage, or prognosis, of lung tumors or colon tumors that amplify the PRO1759 gene compared to lung and colon tumors that do not amplify the PRO1759 gene. It is left to the skilled artisan to determine the significance (if any) of such a difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention. Furthermore, as emphasized by the state of the art (see for example, Madoz-Gurpide et al., Steiner et al, Celis et al, and Feroze-Merzoug et al.), Beer et al. complemented their DNA microarray expression studies with northern blot hybridization and immunohistochemistry experiments for three arbitrarily selected genes with high expression. However, the specification of the instant application does not complement the

low (2-fold) PRO1759 gene expression data with any mRNA or protein studies. The skilled artisan would not reasonably assume that PRO1759 polypeptide is overexpressed in certain lung or cancer tumors based on the disclosure regarding gene amplification without actually testing for PRO1759 polypeptide overexpression. It is also noted that Beer et al. did not examine any expression profiles of the claimed PRO1759 polypeptide or the polynucleotide encoding the polypeptide.

(v) Regarding Hu et al. (cited by Examiner in the previous Office Action), Applicant indicates that among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. Applicant argues that Hu et al. does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels. Applicant contends that since Hu et al. only studies the statistical analysis of microarray data and not the gene amplification data, their findings would not be directly applicable to the gene amplification data. Applicant also states that Hu et al. manipulated various aspects of the input data.

Applicant's arguments have been fully considered but are not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412)

analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. The instant specification does not disclose that PRO1759 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1759 protein can be used as a cancer diagnostic. Regarding Applicant's criticism of Hu et al.'s statistical analysis, Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicant's criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

(vi) Applicant asserts that the Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. Applicant contends that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the

above cited references and application of an improper, heightened legal standard. Applicant states that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

Applicant's arguments have been fully considered but are not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Pennica et al. (cited in the previous Office Action and the Office Action of 04 November 2004), Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associated with breast cancer), Haynes et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al., and Celis et al. These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1759 polypeptide is not useful as a cancer diagnostic agent.

(vii) Applicant indicates that the PRO1759 nucleic acid was amplified in a significant number of lung and colon tumors and showed a large increase in gene copy number, i.e., at least 2-fold amplification. At pages 15-19, and 22-24 of the Response, Applicant argues that the amplification of the nucleic acid encoding the claimed polypeptide is significant for the detection of lung and colon cancer and cite declarations by Dr. Goddard, Dr. Ashkenazi, and Dr. Polakis. However, no substantially new arguments have been presented. These declarations were previously considered and discussed by the Examiner in the Office Action of 25 April 2005.

However, it is again noted that the PRO1759 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1759 nucleic acid was amplified in three cancer samples, to a minor degree (about 2.5 fold). No mutation or translocation of PRO1759 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1759 is expressed in corresponding normal tissues, and what the relative levels of expression are. For example, the gene amplification data presented in the specification were problematic. The control DNA appeared to be from blood rather than from a matched tissue sample (i.e., healthy lung and colon), while the literature shows that matched tissue samples are the standard (Pennica et al.). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen). Therefore, it is not clear that the reported amplification is significant. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1759 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Therefore, based on the totality of the evidence, it is maintained that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO1759 are specifically amplified in lung and colon tumors. Further research would have to be done in order to determine if PRO1759 mRNA and protein are

amplified and, if so, whether or not the amplification is significant enough to reasonably confirm the usefulness of PRO1759 protein as a lung or colon cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

(viii) At pages 19-22 of the Response, Applicant discusses Hanna et al., Orntoft et al., Hyman et al., and Pollack et al. and asserts that they constitute evidence that gene amplification increases mRNA expression levels in general (previously submitted and discussed by Applicant in the previous response of 02 February 2005).

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant comments on the examiner's criticism of Hanna et al., stating that the examiner has misread the reference. Applicant argues that Hanna et al. disclose that gene amplification and protein overexpression are well correlated, and that only a subset of tumors show discordant results. Applicant urge that Hanna et al. support Applicant's position that it is more likely than not that gene amplification correlates with increased polypeptide expression. Applicant asserts that the PRO1759 polypeptide is useful in tumor categorization. Hanna et al. clearly show that the skilled artisan does not assume that any tumor with a HER-2/neu gene amplification event also overexpressed HER-2/neu protein. It is tested empirically. The reason for the testing is irrelevant to the issue at hand. The fact remains that the instant specification does not disclose whether or not PRO1759 protein is overexpressed in any tumors. Therefore, the skilled artisan must perform further research in order to reasonably confirm whether it is or is not. The requirement for such further research indicates that the asserted utility of PRO1759 as a cancer

diagnostic agent is not substantial. The specification does not assert that PRO1759 is useful as an agent to categorize tumors. However, even if it had, the specification does not disclose the expression levels of PRO1759 protein in any tumor samples, so that such would have to be determined through further research on the part of the skilled artisan. Thus, even the utility proposed regarding the usefulness of PRO1759 protein in the categorization of tumors, is not substantial. Finally, there is no disclosure regarding what treatment modality should be chosen by the clinician based on whether or not PRO1759 polypeptide is overexpressed. The determination of such constitutes further experimentation, indicating that the asserted utility is not substantial.

Applicant argues that Orntoft et al. studied 1800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to non-invasive papillomas (also tumors), and then mapped them to chromosomal locations. Applicant argues that the chromosomal locations had already been analyzed for amplification via CGH. Applicant argues that Orntoft et al. found that in general areas with strong gain of chromosomal material contained a cluster of genes having increased mRNA expression. Applicant quotes from Orntoft et al. as stating that a highly significant correlation was observed between the level of CGH ratio change (DNA copy number) and alteration detected by arrays (mRNA levels). Applicant argues that Orntoft et al. studied mRNA relation to protein levels and found a highly significant correlation. Applicant concludes that Orntoft et al. supports Applicant's position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. Applicant also argues that there is no clear relevance of the examiner's concern that PRO1759 has not been disclosed as being part of a gene cluster. This has been fully considered but is not found to be persuasive. Orntoft

et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). Ornitoft et al.'s findings could only be extended to other genes in such clusters. This analysis was not done for PRO1759 in the instant specification, and so it is not clear whether or not PRO1759 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the findings of Ornitoft et al. cannot be extended to PRO1759. Also, Ornitoft et al. compared genes from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison between genes in cancerous versus non-cancerous tissue. Thus, Ornitoft et al. did not find any cancer markers. Furthermore, Ornitoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins. (See abstract). Applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Ornitoft publication) and an associated rise in level of the encoded protein. Finally, Ornitoft et al. did not study lung or colon cancer.

Applicant urges that Hyman et al. and Pollack et al. did not use traditional CGH, but rather did gene-by-gene analysis across all chromosomes. Applicant characterizes Hyman et al. as studying 13,824 clones for gene expression and gene copy number in 14 breast cancer cell lines. Applicant quotes from Hyman et al. regarding their finding that up to 44% of the highly amplified genes were overexpressed compared with only 6% for genes with normal copy number. Applicant further quotes from Hyman et al. regarding the cDNA/microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome. Applicant concludes that Hyman et al. performed an analysis on a gene-by-gene basis, and clearly shows that it is more likely than not that a gene which is amplified in

tumor cells will have increased gene expression. This has been fully considered but is not found to be persuasive. As discussed above, Hyman et al. found 44% (less than half) of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. This is direct evidence that it is "more likely than not" that gene amplification does *not* correlate with increased mRNA expression. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1759 would be correlated with elevated levels of mRNA, much less protein. Also, Hyman et al. did not evaluate lung or colon cancer.

At page 22 of the Response, Applicant characterizes Pollack et al. as studying DNA copy number across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines. Applicant quotes from Pollack et al., saying that parallel microarrays measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells, and that genome-wide, of 117 high-level DNA amplifications, 62% are found associated with at least moderately elevated mRNA levels and 42% associated with highly elevated mRNA levels. Applicant concludes that the Pollack et al. reference constitutes evidence that it is more likely than not that a gene which is amplified in tumor cells will have increased gene expression. This has been fully considered but is not found to be persuasive. As discussed above, Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p.

12965). Pollack et al. is similarly limited to *highly* amplified genes which were not evaluated by the method of the instant specification, and did not test for protein expression levels. Also, Pollack et al. did not study lung or colon cancer.

(ix) Applicant concludes that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1759 gene, that the PRO1759 polypeptide is concomitantly overexpressed. Applicant argues that the claimed PRO1759 polypeptides have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner concedes that the specification teaches how to make PRO1759 polypeptide. However, the specification fails to provide a substantial asserted utility for the claimed PRO1759 polynucleotides, and thus the specification also fails to enable the claimed PRO1759 polypeptides (specifically, the specification fails to teach the skilled artisan how to use the claimed PRO1759 polypeptides without undue experimentation). As discussed above, PRO1759 genomic DNA was found to be slightly amplified in only three out of fifty-two cancer samples compared to a normal DNA control from blood. Gene amplification in lung and colon tumors was not compared to a matched normal tissue samples, as is the standard in the art (see Pennica et al.). The data were not corrected for aneuploidy, which was known to be common in cancerous *and non-cancerous* lung tissue (see Sen). Thus, it is not clear from the gene amplification data whether or not PRO1759 genomic DNA actually is amplified in certain lung or colon tumors. Second, the literature reports that gene amplification often does not correlate

with increased mRNA levels (see Pennica et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al.) or cancerous tissue (see Hu et al., Chen et al., Hanna et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al, Celis et al.). In view of the totality of the evidence, the skilled artisan would not reasonably assume that PRO1759 polypeptide is overexpressed in certain lung or cancer tumors based on the disclosure regarding gene amplification without actually testing for PRO1759 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. Fourth, based on the gene amplification data, the skilled artisan *also* would not presume that PRO1759 polypeptide is *not* overexpressed in certain lung or colon tumors without actually testing for PRO1759 polypeptide levels. In view of such and the lack of guidance regarding how the physician would use information regarding PRO1759 polypeptide overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO1759 polypeptide as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement is proper.

35 U.S.C. § 112, first paragraph (Enablement)

3. Claims 28-35 and 38-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth

at pg 12-15 of the previous Office Action (25 April 2005) and at pg 8-11 of the Office Action of 04 November 2004.

However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-32 and 39-40 would remain rejected under 35 U.S.C. § 112, first paragraph.

Applicant's arguments (21 July 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

It is noted that at pages 25-26 of the Response, Applicant cites pertinent case law reviewing the legal standard of enablement. The Examiner takes no issue with Applicant's general comments regarding the legal standard for enablement.

Applicant argues that the specification teaches specific parameters to be associated with the term "percent identity" and accordingly, one of skill in the art could identify whether the variant PRO1759 native sequence falls within the parameters of the claimed invention. Applicant states that once such an amino acid sequence was identified, the specification sets forth methods for making, preparing, and testing the amino acid sequences. Applicant submits that one skill in the art could practice the claimed invention without undue experimentation. Applicant also contends that the claims are directed to native sequence polypeptides and thus the nature of the changes to the polypeptide sequence have already been determined by natural evolutionary processes and need not be tested by the skilled artisan. Applicant states that the claims recite polypeptide sequences associated with a biological activity and that this biological activity together with the well defined high degree of sequence identity and knowledge in the art defines the claimed genus such that one of skill in the art would have known how to make and

use the claimed polypeptide sequences without undue experimentation. Applicant adds that a considerable amount of experimentation is permissible, if it is routine.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Appellant's arguments have been considered but are not found to be persuasive because the broad brush discussion of making and screening for allelic variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the PRO1759 polypeptide of SEQ ID NO: 374 is disclosed. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such trial and error experimentation is considered undue.

Certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan

to generate the infinite number of derivatives recited in the claims and screen the same for activity.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 112, first paragraph (written description)

4. Claims 28-32 and 39-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 15 of the previous Office Action of 25 April 2005 and at pg 11-13 of the Office Action of 04 November 2004.

Applicant's arguments (21 July 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

It is noted that at pages 29-30 of the Response, Applicant cites pertinent case law reviewing the legal standard of written description. The Examiner takes no issue with Applicant's general comments regarding the legal standard for written description.

Applicant argues that claims 28-32 have been amended to recite an isolated native sequence polypeptide. Applicant contends that the genus of native sequence polypeptides with at least 80% sequence identity to SEQ ID NO: 354, which possess the functional property of having a nucleic acid which is amplified in lung or colon tumors would meet the requirement of 35 U.S.C. § 112, first paragraph, as providing written description. Applicant argues that the specification teaches specific parameters to be associated with the term "percent identity" and accordingly, one of skill in the art could identify whether the variant PRO1759 native sequence falls within the parameters of the claimed invention. Applicant states that once such an amino acid sequence was identified, the specification sets forth methods for making, preparing, and testing the amino acid sequences.

Applicant's arguments have been fully considered but are not found to be persuasive. The courts have specifically stated that the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide until the structure is disclosed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Applicant has not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID

NO: 374, that still retain the function of SEQ ID NO: 374. Nor has Applicant described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 374, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 374. Even one skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed PRO1759 polypeptides, and therefore, would not know how to make or use them.

The broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the PRO1759 polypeptide of SEQ ID NO: 374 is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. Additionally, no native sequence variant of PRO1759 have been disclosed regardless of whether or not they are encoded by nucleic acids that are amplified in tumors. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity, a requirement that the sequence be native, and a requirement that the encoding nucleic acids are amplified in lung or colon tumors. There is no identification of any particular portion of the structure that must be

conserved in order to conserve the required function. Additionally, there is the issue of whether or not the single disclosed embodiment is actually amplified in lung or colon tumors (see rejection under 35 U.S.C. §§ 101 and 112, first paragraph, above). Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
28 September 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER